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Synopsis of Scientific Literature on Phenoxy Herbicides and Associated Dioxins No. 6 – (Volumes XIII and XIV)

Veterans Health Services
and Research Administration

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**SYNOPSIS OF SCIENTIFIC LITERATURE
ON PHENOXY HERBICIDES
AND ASSOCIATED DIOXINS
NO. 6 – (Volumes XIII and XIV)**

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PREFACE

This synopsis is the sixth in a series of lay language summaries of the *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. Synopsis No. 1 of Volumes I and IV was published in July 1985, Synopsis No. 2 of Volumes V and VI was published in October 1985, Synopsis No. 3 of Volumes VII and VIII was published in October 1986, Synopsis No. 4 of Volumes IX and X was published in July 1987, and Synopsis No. 5 of Volumes XI and XII was published in September 1988.

This Current synopsis, a review of Volumes XIII and XIV, continues the effort of the Department of Veterans Affairs to provide for the general public a summary in laymen's terms, of the scientific literature published during 1988 related to the possible health effects of exposure to phenoxy herbicides and dioxins.

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1. Introduction

In May 1989, Clement Associates, Inc., a research firm in Fairfax, Virginia, completed a review of the literature published during 1988 on the health effects of Agent Orange and related compounds. A critical review and an annotated bibliography of this literature have been published as Volumes XIII and XIV of the ongoing *Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins*. The present synopsis summarizes the key new information that became available during 1988.

Phenoxy herbicides are a group of structurally related chemicals that have been used to kill plants, including trees. They have been used in agriculture and forestry to kill weeds in cultivated crops, to kill unwanted tree species in coniferous forests, and to clear plant growth from road beds and fence lines. Historically, the phenoxy herbicides that have been most frequently used in the United States are 2,4-D and 2,4,5-T. The latter is no longer used in this country. Several herbicidal preparations were used from 1963 to 1971 during the military action in Vietnam, primarily to remove leaves from jungle trees to allow the observation of enemy troop movements from the air. The application of these herbicides was conducted by the U.S. Air Force in a program known as Operation Ranch Hand. Agent Orange, a mixture of equal parts of 2,4-D and 2,4, 5-T, was the herbicide that was used most frequently.

Commercial phenoxy herbicides manufactured in the past contained small but variable quantities of contaminating impurities known as chlorinated dibenzo-p-dioxins. The term "dioxins" has frequently been used as shorthand for these compounds. It is known that very small amounts of one of these dioxins, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), were present in the 2,4,5-T portion of the Agent Orange used in Vietnam; it was not present in 2,4-D. The effects of TCDD have been studied extensively in experimental animals. Some other herbicides that were used in Vietnam are cacodylic acid and picloram. However, they were used in much smaller quantities and were not contaminated with dioxins.

2. Description of the literature published in 1988

Just over 300 scientific articles about the health effects of phenoxy herbicides, dioxins, and related herbicides were published in 1988. This is about the same number of articles as were published in each of the two previous years. This suggests that scientific interest in this subject has not diminished. Of these publications about one third were abstracts and the remainder were full length articles.

As in the previous three years, an increasing percentage of the literature describes the results of studies of the effects of TCDD and related compounds in experimental animals. The results of these studies have little immediate relevance to the expected health effects of phenoxy herbicides in humans. However, scientists believe that once they understand how dioxin causes its effects in experimental animals, they will be able to predict more accurately the effects that are likely to occur in humans exposed to these compounds. Because some or all of the human health effects of phenoxy herbicides may be caused by

their dioxin impurities, this information may become important in the future. No articles were published in 1988 that contained information on the potential health effects of cacodylic acid or picloram. A relatively large number of articles was published on the measurement of dioxins in blood and fat of humans who may have been exposed to phenoxy herbicides or dioxins.

3. Health studies among Vietnam veterans

In the late 1970s, the American public became interested in the possible long-term health effects of military service in Vietnam. One aspect of this concern was that American servicemen who were exposed to herbicides in Vietnam might develop lasting adverse health effects that first appeared after the veterans had returned home. In 1979 and 1981 Congress ordered the Veterans Administration (now the Department of Veterans Affairs) to investigate the possible long-term health effects of military service in Vietnam, especially those effects that might have resulted from exposure to the herbicide known as Agent Orange. As part of this investigation the Department of Veterans Affairs (VA) initiated a series of epidemiology (human health effect) studies. Because veterans' advocacy groups doubted the objectivity of the VA, the responsibility for the conduct of some of these epidemiology studies was turned over to the U.S. Centers for Disease Control (CDC) in 1983.

The CDC undertook several major epidemiology studies of Vietnam veterans. One of these was designed to compare the health of Vietnam veterans with the health of veterans of the U.S. armed forces who served in locations other than Southeast Asia during the Vietnam era. This study, which is known as the Vietnam Experience Study (VES), was intended to see if there were any lasting health consequences of military service in Vietnam. It was not the intent of this study to link health effects to any specific aspect of Vietnam service such as exposure to herbicides or combat involvement. The results of the VES were published in 1988.

Another study considered by the CDC was the Agent Orange Exposure Study (AOES). This study was designed to relate the current health status of Vietnam veterans to their exposure to herbicides, including Agent Orange, in Vietnam. In order for the AOES to be successful, it was necessary to assess accurately herbicide exposure among Vietnam veterans 10 – 20 years after the fact. To do this, CDC attempted to combine information on the dates and locations of herbicide application missions with information on troop locations from individual veteran's military service records, in order to derive a herbicide exposure index for each veteran in the study. Veterans in the study were also asked to estimate their herbicide exposure based on their memory of being in an area when spraying took place. Altogether, five different methods of developing a herbicide exposure index were used to estimate herbicide exposure among a pilot study population of 665 Vietnam veterans and 103 non-Vietnam veterans. No correlation was found among the various indices of exposure.

The CDC made a further attempt to assess herbicide exposure by measuring the concentration of dioxins in the blood of Vietnam veterans. The results of this study were published in 1986 and 1987 and have been described in previous volumes of this synopsis. The CDC found no correlation between

present concentrations of dioxins in veterans' blood and any other estimate of herbicide exposure except for those relatively few veterans who actually participated in herbicide application. The CDC has concluded that it is impossible to assess accurately herbicide exposure in Vietnam. This conclusion has been reviewed by a number of expert advisory committees and based on their concurrence the AOES has been canceled. This decision has been disputed by several veterans' advocacy groups.

A third study undertaken by the CDC was the Selected Cancers Study. This case-control study is designed to determine whether the risk for specific types of cancer are greater among Vietnam veterans and whether these elevated risks (if any) are related to any specific aspect of their service in Vietnam, including exposure to herbicides. This study is still in progress and is expected to be published in 1990.

At about the time the responsibility for these epidemiology studies was shifted from VA to CDC, the American Legion (a veterans service organization) decided to sponsor an independent epidemiology study of the long-term health consequences of military service in Vietnam. This study was completed in 1984 and the results were published in 1988.

There are important similarities and differences in the methods and objectives of the VES and the American Legion study. Both studies measured current and past health status among Vietnam veterans and compared it to that of veterans of the same era who served in locations other than in Southeast Asia. Both studies used questionnaires to assess current health status. In the American Legion study, the questionnaire was a self-administered written questionnaire. In the VES, the subjects were interviewed by telephone by trained interviewers who were prompted by computer. A random subsample of veterans selected for the VES were invited to undergo a complete physical and medical examination. None of the subjects in the American Legion study was examined or tested.

In the VES study, a random sample of military records was used to identify a study population of U.S. Army enlisted men who had served in Vietnam and a control population of U.S. Army enlisted men who had served elsewhere during the same era. The subjects in the American Legion study were selected from the active membership of the American Legion in six states and were enrolled in the study by "volunteer researchers" who were assigned the task of identifying 15 Vietnam veterans and 15 non-Vietnam veterans for the study. This creates the possibility that the veteran who participated in the American Legion study were not representative of all U.S. veterans.

For the most part, the health status of Vietnam veterans in the VES was compared to that of non-Vietnam veterans in order to assess the consequences of the Vietnam experience as a whole. A few comparisons were made on the basis of the veterans' recall of herbicide exposure and/or combat experience. The American Legion study, on the other hand, attempted to characterize both herbicide exposure and combat exposure among the Vietnam veterans and to relate health effects to those exposures. Combat exposure was derived from the answers to eight questions in the questionnaire. The method used to assess herbicide exposure was less rigorous than that attempted and abandoned as invalid by the CDC in the AOES. No attempt was made in the American Legion study to validate herbicide exposure estimates

using military service records or by measuring levels of dioxin in blood. Both the Office of Technology Assessment and the Science Panel of the Agent Orange Working Group have criticized the American Legion study because of the questionable validity of the herbicides exposure index.

Despite the differences between these studies and the controversy surrounding their methodology, both the VES and the American Legion study convincingly demonstrated that Vietnam veterans report more current and past health problems than non-Vietnam veterans. They also report more adverse reproductive outcomes and more health problems among their children. In the VES, reported adverse health status was associated with recall of herbicide exposure among Vietnam veterans. Those Vietnam veterans who did not think they were exposed to herbicides in Vietnam reported no more health problems than did non-Vietnam veterans. In the American Legion study the perception of poor health among Vietnam veterans was associated with both combat and herbicides exposure as assessed by the questionnaire. This study also showed a strong correlation between reported combat exposure and herbicide exposure making it difficult to independently assess the impact of either of these by itself.

The physical and medical examination and testing that was performed on some of the participants in the VES failed to confirm the adverse health effects that were reported in the telephone interviews. The only difference between Vietnam and non-Vietnam veterans revealed by the medical examination were hearing loss, the presence of blood in feces, lower sperm counts, and altered sperm morphology. None of these were related to health effects reported during the telephone interviews. There was no evidence of differences in fertility or reproductive success associated with the differences in sperm characteristics.

Both the VES and the American Legion study showed major differences between Vietnam veterans and non-Vietnam veterans with regard to psychological well-being. The American Legion study showed a much greater prevalence of symptoms characteristic of post traumatic stress disorder (PTSD) among Vietnam veterans than among non-Vietnam veterans. Neurologic function tests performed in the VES showed no differences between Vietnam and non-veterans.

Taken together, the VES and the American Legion study indicate that Vietnam veterans perceive themselves to be in poorer health than non-Vietnam veterans. The American Legion study indicates that this perception may correlate with subjective and unvalidated assessment of exposure to herbicides and/or combat. The VES suggests that most of the perceived adverse health effects cannot be confirmed objectively by medical examination. The perception of poor health is important of and by itself and a biochemical basis for this perception cannot be ruled out.

A study of causes of death among veterans in Wisconsin became available during 1988. In this study causes of death among Vietnam veterans were compared to causes of death among non-Vietnam veterans of the same era, among all military veterans and among all males in Wisconsin. The results of this study were consistent with similar studies among Vietnam veterans. Vietnam-era veterans were more likely to die of all external causes (accidents, homicide, and suicide) than were veterans of other eras

and non-veterans. Vietnam veterans were more likely to die of accidents than non-Vietnam veterans. Vietnam veterans were more likely to die from accidents and suicide than any other comparison group. There was no evidence of excess deaths due to cancer among Vietnam veterans. However, there were too few cases of cancer to allow comparisons for specific types of cancer. There was no attempt to determine herbicide exposure in this study.

4. Cancer

No studies of possible relationships between cancer and herbicide exposure in Vietnam became available during 1988. Over the past ten years there have been isolated studies that suggested associations between the agricultural use of herbicides and certain forms of cancer. Some of the most frequently cited of these were studies conducted in Sweden nearly ten years ago that suggested an association between exposure to phenoxy herbicides and a class of cancers known as soft-tissue sarcomas. Because of persistent criticisms and the inability of other investigators to duplicate these results, the authors repeated this study and the results were published in 1988. The new study also showed an association between soft-tissue sarcomas and exposure to phenoxy herbicides but the increased risk was smaller than in the earlier studies. Questions about the determination of herbicide exposure that were raised by the original study apply to this study as well. Two additional epidemiologic studies conducted among agricultural workers in Sweden failed to show any association between herbicide exposure and another form of cancer, non-Hodgkin's lymphoma.

Two epidemiology studies conducted at the Dow Chemical Company in Midland, Michigan found no cases of soft-tissue sarcoma or non-Hodgkin's lymphoma among workers involved in the manufacture of 2,4-D or among workers who had a history of chloracne probably from being exposed to dioxins at the plant many years ago. Workers involved in the manufacture of 2,4-D did have an excess of cancers at ill-defined sites but the significance of this finding is questionable in that this tumor classification is a catch-all category of cancer types that may not be biologically related to each other. The workers with a history of chloracne did not have any excess risk of cancer but there was an excess risk of death due to strokes in this group of workers.

A preliminary report of an epidemiology study of causes of death among people who consumed cooking oil heavily contaminated with polychlorinated biphenyls and chlorinated dibenzofurans (structural relatives of dioxins) in an incident in Japan in 1968 suggested that there might be an increased risk of liver cancer among these people. This was accompanied by an increased number of deaths due to non-cancerous liver disease. This preliminary and unconfirmed finding is nevertheless interesting in that these compounds damage the liver and cause liver cancer when they are fed to experimental animals. The compounds themselves were not, however, used in Vietnam.

A summary report of an industry task force indicated that there was an increased incidence of a type of brain tumor in rats given oral doses of 2,4,-D for most of their lifetimes. The authors of the summary report indicated that this finding was "not biologically significant". A full report describing the

methods and results of this study has not been published and therefore the conclusions of the industry task force cannot be independently evaluated.

Taken together, the results of studies of the relationship between exposure to herbicides and or their contaminating dioxin impurities and cancer continue to be inconclusive but in general the weight of evidence goes against such an association. The studies conducted by Dow Chemical Company are particularly important because the workers who were studied were both relatively heavily exposed and many of them were exposed a number of years ago so that delayed effects would have a chance to appear. Nevertheless, because of the relatively small number of workers involved only marked increases in risk would be expected to be apparent. These groups need to be followed well into the future.

5. Genetic effects

No new studies of the potential genetic effects of phenoxy herbicides or their dioxin impurities were published in 1988. Several laboratory studies in which 2,4,-D, 2,4,5-T, and TCDD were tested for their ability to cause mutations in bacteria and individual cells in culture were negative. These studies support the findings of a large number of earlier studies that indicate that none of these compounds possess the ability to cause gene mutations. One study published in 1988 did find that 2,4-D damaged chromosomes in the bone marrow of rats but the human health significance of this finding is unclear.

6. Reproductive and teratogenic effects

The results of the telephone interview in the VES described above indicated that Vietnam veterans reported more adverse reproductive and child health outcomes than did non-Vietnam veterans. A review of hospital birth records, however, indicated that Vietnam veterans were not at increased risk of fathering children with birth defects. A subsample of Vietnam veterans in the VES did have lower sperm counts and altered sperm morphology compared to a similar group of non-Vietnam veterans but this effect did not translate into reduced success in fathering healthy children. In the American Legion study the self-administered questionnaire did not contain questions designed to identify birth defects among the children of veterans. Answers to questions indicated that there was no association between reported herbicide exposure index and difficulty of conception, time to first conception, birth weight, or sex ratio of children among Vietnam veterans. This study did indicate that miscarriage rate was associated with the exposure index. In view of the questionable validity of the exposure index and the unreliability of father's recall regarding miscarriages, little significance can be attached to this reported finding.

An epidemiology study of birth outcomes in an agricultural area of New Brunswick, Canada suggested a possible association between exposure of the general population to agricultural chemicals, in general, and the incidence of birth defects and stillbirths. However, the lack of information on specific agricultural chemicals used render these findings irrelevant to the question of the health effects of phenoxy herbicides. Two surveys of reproductive outcomes in geographic areas where there had been

significant episodes of contamination of the environment with dioxins found no excess of adverse reproductive effects. On the other hand a study of children born to women in Taiwan who had consumed cooking oil that was heavily contaminated with polychlorinated biphenyls and chlorinated dibenzofurans in 1979 revealed a wide spectrum of adverse effects including low birthweight, dark skin, inflammation of the eyelids, neurological defects, and abnormal teeth, nails, and gums. These children also had delayed development and displayed abnormal behavior. It must be emphasized that the quantities of dibenzofurans consumed by the mothers were sufficiently large to cause symptoms of acute toxicity in the mothers themselves and are far higher than quantities of dioxins that might be encountered from environmental sources. None of these compounds were used or contaminated food sources in Vietnam.

The results of several studies in experimental animals indicate that relatively large amounts of 2,4-D and 2,4,5-T produce neurological and behavioral effects in newborns. A number of studies of the effects of TCDD in experimental animals indicate that this compound changes the way normal sex hormones such as estrogen and testosterone work in the body. It is not yet fully understood how these interactions may be manifested and whether they are directly relevant to human health. This question is likely to be the subject of much future research.

7. Effects on the immune system

In the VES, tests designed to assess the status and function of the immune system showed no differences between Vietnam and non-Vietnam veterans. Continuing studies of people who live in an area of Missouri where there were relatively high levels of dioxin in the soil showed slight differences in the relative numbers of certain types of blood cells that are associated with the immune system but these differences were not associated with any measurable differences in immune function.

8. Neurobehavioral effects

Both the VES and the American Legion study showed that the psychological well-being of Vietnam veterans is impaired compared to non-Vietnam veterans of the same era. However, there is no objective evidence that this is associated with herbicide exposure. Tests of neurological function in the VES did not show any differences between Vietnam veterans and non-Vietnam veterans. Measures of neurologic function in residents of Seveso, Italy showed no differences between people who were probably exposed to dioxin contamination and those who probably were not exposed.

9. Other toxic effects

Three case reports of near fatal intoxication caused by the intentional ingestion of large quantities of phenoxy herbicides indicate that acute poisoning with these compounds consists of prompt and

severe central nervous system depression leading to respiratory failure and coma. These compounds also attack the musculoskeletal system causing a breakdown of muscle tissue and subsequent kidney failure.

A brief abstract indicated that exposure of workers to dioxins in the workplace might cause alterations in blood flow to the brain. Although this finding requires independent confirmation it is interesting in view of the finding of an increased risk of strokes among workers with a history of chloracne of the Dow Chemical facility.

10. Tissue residues of chlorinated dibenzo-p-dioxins

The results of studies that were published in 1988 confirmed preliminary reports that the concentrations of dioxins in blood samples from Vietnam veterans were not different from those in blood samples from non-Vietnam veterans or the general population. While a few individuals who may have been heavily exposed to phenoxy herbicides in Vietnam have elevated concentrations of dioxin in their blood up to 20 years after exposure, this approach is not useful for assessing relative herbicide exposure among a sufficiently large population of Vietnam-era veterans for a definitive epidemiologic study of associations between herbicide exposure and health effects. Similar studies of dioxin concentrations in blood were unsuccessful in identifying a "dioxin-exposed" population of people living in areas of Missouri that were relatively contaminated with dioxins.

Certain groups of individuals who have been heavily exposed in the past, specifically individuals who were actually engaged in herbicides application in Vietnam and people who were heavily exposed to dioxin as a result of the ICMESA plant accident in Seveso, Italy in 1976 have elevated concentrations of dioxin in the blood many years after the exposure. The results of the study of the Seveso population suggest, however, that present concentrations of dioxins in the blood are not strictly correlated with the severity of the symptoms seen at the time of the accident. This may indicate differential sensitivity to the effects of dioxin among individuals, differential rates of elimination of dioxin from the body or both. Many studies also indicate that individuals with no extraordinary exposure to dioxins or phenoxy herbicides have measurable levels that tend to increase with age. This suggests that the general population is continuously exposed to small amounts of dioxin from environmental sources.

11. Summary and conclusions

The volume of scientific literature relevant to the health effects of phenoxy herbicides and their contaminating dioxin impurities published during 1988 was similar to that of the preceding two years indicating undiminished scientific interest in this subject. A large portion of the literature described studies of the mechanism by which dioxins and related compounds cause biological effects in experimental animals. At the present time, these studies are of limited relevance for assessing the human health effects of exposure to herbicides in Vietnam but may lead, in the future, to a better understanding of how these

compounds cause adverse health effects in animals and humans. No literature relevant to the human health effects of other herbicides used in Vietnam, i.e., picloram and cacodylic acid, was published during 1988.

The results of two large epidemiologic studies of the current health status of veterans who served in Vietnam were published during 1988. Both of these studies showed that Vietnam veterans report more current and past health problems than non-Vietnam veterans. Vietnam veterans also report more adverse reproductive outcomes and more health problems among their children. In both studies, the perception of poor health was correlated with the veterans' belief that they were exposed to herbicides in Vietnam. However, in the absence of a valid means of assessing herbicide exposure, the relationship between perceived health status and herbicide exposure could not be verified objectively. In the one study where the subjects underwent psychological and medical examinations, few differences in health status could be found between Vietnam and non-Vietnam veterans. Both studies showed major differences between Vietnam veterans and non-Vietnam veterans with regard to psychological well-being.

A mortality study conducted among Vietnam veterans in Wisconsin indicated that Vietnam veterans were more likely to die of accidents and suicide than were men in any other comparison group and were more likely to die of accidents than non-Vietnam veterans. There was no evidence of excess deaths due to cancer among Vietnam veterans. Taken together all of these studies indicate that Vietnam veterans are different from non-Vietnam veterans with regard to perceived current health status, psychological well-being, and mortality patterns. However, these studies do not indicate what aspect(s) of the Vietnam experience are responsible for these differences. Neither medical and physical examinations nor mortality rates confirmed the differences that Vietnam veterans reported in current health status as compared to the health of non-Vietnam veterans.

Epidemiologic studies of possible association between exposure to phenoxy herbicides or their contaminating dioxin impurities and cancer continued to give inconsistent results. A case-control study of soft-tissue sarcoma by the Swedish investigators who first reported such a relationship indicated a significant association of this class of cancers with recalled exposure to phenoxy herbicides. Several other epidemiologic studies of cancer among agricultural workers and workers at a chemical factory who were exposed to 2,4,-D and/or to dioxins indicated no increased risk of cancer associated with these exposures. Workers with a history of possible exposure to dioxins did have an increased risk of death from strokes, however. Additional research is required before any conclusions regarding cause and effect can be reached.

Vietnam veterans who participated in the American Legion study reported that a higher proportion of their reproductive attempts resulted in miscarriage than did non-Vietnam veterans but no attempt was made to verify this perception of objective methods. There was no association between estimated herbicide and/or combat exposure and any other reported indicator of reproductive success in the American Legion study. A subsample of Vietnam veterans in the VES had lower sperm counts and altered sperm morphology when compared to a similar group of non-Vietnam veterans. These differences were not correlated with any indicators of reproductive success within the cohort, however.

The few studies of the genetic effects of phenoxy herbicides and dioxins that were published in 1988 confirmed earlier findings that these compounds are not directly mutagenic. One study did indicate that 2,4-D may damage chromosomes in rats. Studies in experimental animals indicated that doses of 2,4-D and 2,4,5-T sufficient to cause acute toxicity in pregnant females produced adverse neurological and behavioral effects in their offspring. Also a number of studies in experimental animals indicated that dioxins change the way normal sex hormones such as estrogen and testosterone work. The relevance of these findings to human health is not yet clear.

There were no differences between Vietnam veterans and non-Vietnam veterans in the status and function of the immune system in the one epidemiologic study where the immune system was evaluated. A study of people exposed to dioxin contaminated soil in Missouri found differences in the relative proportions of certain blood cells that are associated with the immune system but these differences were not accompanied by differences in immune function.

Studies of dioxin concentrations in blood or fat of people exposed to these compounds in the past indicated that elevated concentrations of these compounds are present in the tissue of people who were heavily exposed, e.g. Vietnam veterans who were actually involved in herbicide application and residents of the Italian community of Seveso, who developed chloracne from exposure to dioxins as the result of an industrial accident in 1976. However, measurement of the concentration of dioxin in the blood was not useful for identifying individuals who may have been less heavily exposed in the past such as Vietnam ground troops because these concentrations were not different from background levels. Furthermore, limited evidence suggests that there is a great deal of variability among individuals in both their background exposure to dioxins and in the rates with which it is eliminated from the body. This would suggest that generalized quantitative correlations between current body burdens and past exposure cannot be established.

In general, the scientific literature published during 1988 was similar to that published in the preceding few years and primarily served to corroborate what was already known. Two major studies of the current health status of Vietnam veterans served to point out many of the difficulties inherent in attempting to relate lasting adverse health effects to any specific aspect of the Vietnam experience, including herbicide exposure. While Vietnam veterans, as a group clearly perceive themselves to be in poorer health than non-Vietnam veterans, this difference cannot be verified upon physical and medical examination nor can it be associated with any specific aspect of the Vietnam experience such as herbicide exposure. Other studies continue to provide conflicting evidence with regard to possible relationships between exposure to phenoxy herbicides and their dioxin impurities and such effects as cancer, reproductive effects, and alterations in the immune system, but the overall weight of evidence favors the view that risks of these effects are not markedly elevated in individuals exposed to these compounds.